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6784155.pn. and caso\$	1

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<u>L14</u>	6784155.pn. and caso\$	1	<u>L14</u>
<u>L13</u>	L12 and caso\$	1	<u>L13</u>
<u>L12</u>	6784155.pn. and blood	2	<u>L12</u>
<u>L11</u>	L10 and (heart or blood or cardio\$ or arter\$)	88	<u>L11</u>
<u>L10</u>	(casomorphin or caseomorphine)	114	<u>L10</u>

*DB=USPT,USOC,EPAB,JPAB,DWPI; PLUR=YES; OP=ADJ*

<u>L9</u>	L7 same cardio\$	2	<u>L9</u>
<u>L8</u>	L7 and cardio\$	15	<u>L8</u>
<u>L7</u>	casomorphin	69	<u>L7</u>
<u>L6</u>	L5 and cardio\$	0	<u>L6</u>
<u>L5</u>	caseomorphine	4	<u>L5</u>
<u>L4</u>	l1 and cardio\$	15	<u>L4</u>
<u>L3</u>	l1 and cardiovascular	9	<u>L3</u>
<u>L2</u>	\$casomorphin 9	0	<u>L2</u>

L1 Scasomorphin

57 L1

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L11: Entry 75 of 88

File: USPT

Apr 14, 1998

DOCUMENT-IDENTIFIER: US 5739407 A

TITLE: Human .beta.-casein, process for producing it and use thereof

Brief Summary Text (10):

Soy-protein formulas, although different in carbohydrate and protein source, are similar in composition to cow's milk protein formulas following the American Academy of Pediatrics, Committee on Nutrition recommendations for nutrient levels in infant formulas. Differences include a slightly higher protein level and slightly lower carbohydrate content. The protein source is generally soy-protein; the fat is a blend of vegetable oils; and the source of carbohydrate is usually sucrose, corn syrup solids, or a mixture of both. However, the use of soy formulas tends to raise serum alkaline phosphatase and blood urea levels in infants in addition to causing the allergic and digestibility problems encountered with the use of bovine-based protein infant formulas.

Brief Summary Text (12):

.beta.-Casein is a phosphorylated protein which is present in milk of several species, including humans in which it is the major casein subunit. This protein--or its digested fragments--is believed to enhance calcium absorption by chelating calcium to its phosphorylated residues and thereby keeping it in an absorbable form. Human .beta.-casein is easily digested by newborn infants and the digestive products have been found to play an important role in the calcium uptake, and thus in the mineralization of the skeleton. A digestion product (.beta.-casomorphin) of human .beta.-casein has been found to have opioid activity and may be involved in the sleeping patterns of breast-fed infants.

Brief Summary Text (32):

The term "calcium-binding activity" denotes the capability of the polypeptide of the invention to bind calcium and may be determined by equilibrium dialysis or a similar technique. The term is to be understood in the sense that the polypeptide in question is capable of binding calcium by the same or substantially the same mechanism as human .beta.-casein; however, the term does not necessarily indicate that the binding is quantitatively the same, considering, inter alia, that the calcium binding capability is dependent on the degree of phosphorylation, which, on its side, may differ considerably dependent on the species in which the recombinant polypeptide is produced. The term "opioid activity" denotes the peptide's opiate-like effects and capability of the peptide to bind to opiate receptors (opiate receptor affinity). The "opioid activity" is determined as disclosed by Brantl, 1984 and Migliori-Samour et al. The term "ACE-inhibitory activity" denotes the capability of the peptide to inhibit the angiotensin converting enzyme (ACE) and has important indications for the treatment of heart disorders. The ACE-inhibitory effect is determined by use of a method as disclosed by Maruyama et al. and Kohmura et al.

Detailed Description Text (5):

Brantl, V. Novel opioid peptides derived from human .beta.-casein: Human .beta.-casomorphins. Eur. J. Pharmacol. 106, 213-214, 1984.

Other Reference Publication (10):

V. Brantl, "Novel Opioid Peptides Derived From Human Beta-Casein: Human Beta-

Casomorphins", European Journal of Pharmacology; vol. 106, pp. 213-214 (1985).

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# analogue

<chemistry> A compound that is structurally similar to another.

(10 Jan 1998)

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**Previous:** [anallergic](#), [anal membrane](#), [analog](#), [analog-digital conversion](#), [analogous](#)

**Next:** [analogy](#), [anal orifice](#), [analphalipoproteinaemia](#), [anal phase](#), [anal pit](#)

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☐ 1: Life Sci. 1980 May 5;26(18):1517-22.

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## Cardiovascular effects of peptides related to the enkephalins and beta-casomorphin.

Wei ET, Lee A, Chang JK.

PMID: 7392801 [PubMed - indexed for MEDLINE]

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Nov 23 2004 06:26:50



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## Effect of beta-casomorphin and its analogue on serum prolactin the rat.

Nedvidkova J, Kasafirek E, Dlabac A, Felt V.

The effects of exogenous opioid peptides beta-casomorphin Tyr-Pro-Phe-Pro Gly-Pro-Ile and its analogue Tyr-Pro-Gly-Pro-Phe-Pro-Ile (analogue I) were found to increase prolactin level in plasma after intraperitoneal injection. Analogue I was more potent. This effect of beta-casomorphin and analogue I were blocked by an opioid antagonist, naloxone. These results indicate that the exogenous opioid peptides (exorphins) may participate in the regulation of prolactin secretion. The similarity of analogue I with enkephalin structure was discussed.

PMID: 4018163 [PubMed - indexed for MEDLINE]

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<u>L6</u>	L5 and cardio\$	0	<u>L6</u>
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<u>L4</u>	11 and cardio\$	15	<u>L4</u>
<u>L3</u>	11 and cardiovascular	9	<u>L3</u>
<u>L2</u>	\$casomorphin 9	0	<u>L2</u>



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L1 QUE (CASOMORPHIN OR CASEOMORPHINE) (10W) (9 OR NINE) (P) (CARDIO? OR HEART)  
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FILE 'CAPLUS, FROSTI' ENTERED AT 18:14:46 ON 06 DEC 2004

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L3 4 DUP REM L2 (0 DUPLICATES REMOVED)  
D IBIB ABS L3 1-4  
L4 1 SEA (CASOMORPHIN OR CASEOMORPHINE) (3W) (ANALOG?) (P) (HEART OR CARDIO?)  
D IBIB ABS L4  
L5 19 SEA (CASOMORPHIN OR CASEOMORPHINE) (P) (HEART OR CARDIO?)  
L6 19 DUP REM L5 (0 DUPLICATES REMOVED)  
D IBIB ABS L6 1-19

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L7 4 SEA (CASOMORPHIN OR CASEOMORPHINE) (3W) (ANALOG?) (P) (CARDIO? OR HEART)  
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L2 4 L1

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L3 4 DUP REM L2 (0 DUPLICATES REMOVED)

=> d ibib abs l3 1-4

L3 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1990:179897 CAPLUS  
DOCUMENT NUMBER: 112:179897  
TITLE: Preparation of casomorphin analogs as cardiovascular agents  
INVENTOR(S): Neubert, Klaus; Mentz, Peter; Barth, Alfred; Liebmann, Claus; Schrader, Uwe; Hartrodt, Bianka; Born, Ilona; Luecke, Lothar; Stoeckel, Christian; et al.  
PATENT ASSIGNEE(S): VEB Fahlberg-List, Ger. Dem. Rep.  
SOURCE: Ger. (East), 23 pp.  
CODEN: GEXXA8  
DOCUMENT TYPE: Patent  
LANGUAGE: German  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DD 272227	A1	19891004	DD 1988-315831	19880517
PRIORITY APPLN. INFO.:			DD 1988-315831	19880517

OTHER SOURCE(S): CASREACT 112:179897

AB **Cardioactive** preps. containing **casomorphin** analogs at 10-9-10-7M were prepared Thus, H-Tyr-Pro-D-Phe-Pro-Gly-OH.HCl, prepared by the solution phase method, at 10-9M in guinea pig auricle increased cardiac performance (product of contractile amplitude and frequency) by 20%.

L3 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1987:44286 CAPLUS  
DOCUMENT NUMBER: 106:44286  
TITLE: Effects of  $\beta$ -casomorphin on 3H-ouabain binding to guinea pig heart membranes  
AUTHOR(S): Liebmann, C.; Barth, A.; Neubert, K.; Mentz, P.; Hoffmann, S.  
CORPORATE SOURCE: Dep. Biol., Friedrich-Schiller-Univ., Jena, DDR-4020, Ger. Dem. Rep.  
SOURCE: Pharmazie (1986), 41(9), 670-1  
CODEN: PHARAT; ISSN: 0031-7144  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB  $\beta$ - **Casomorphin** 5 (I) [72122-63-5] at low concns. (10-9-3 + 10-7 M) increased the binding of ouabain [630-60-4] to guinea pig cardiac cell membranes, but higher concns. (10-6-10-4 M) diminished the binding. Since I reputedly has a pos. inotropic effect on isolated hearts at low doses and a **cardiodepressive** action at higher doses, results are consistent with the concept that pos. inotropy is associated with an inhibition of the Na pump. Ouabain binding was not greatly altered by dihydromorphine [509-60-4] or D-Ala2-Leu5-enkephalin [64963-01-5], indicating that the effect of I was not mediated by  $\mu$ - or  $\delta$ -type opiate receptors.

L3 ANSWER 3 OF 4 FROSTI COPYRIGHT 2004 LFRA on STN

ACCESSION NUMBER: 583193 FROSTI  
TITLE: Prophylactic dietary supplement based on milk.  
INVENTOR: Elliott R.B.; Laugesen B.M.  
PATENT ASSIGNEE: New Zealand Milk Institute Ltd  
SOURCE: European Patent Application  
PATENT INFORMATION: EP 1196047 A1  
WO 2001000047 20010104  
APPLICATION INFORMATION: 20000629  
PRIORITY INFORMATION: New Zealand 19990629; 20000418  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
SUMMARY LANGUAGE: English  
AB A fortified milk product is described, for use as a dietary supplement.

It contains cobalamin (vitamin V12), pyridoxine, folic acid, and betaine, with a casein fraction limited to Type 2 casein. The invention provides for manufacture of treated milk products and cereals. The supplement is intended to be used in control of diabetes and in reducing risk of **cardiovascular** disease. This may be achieved by treating an underlying deficiency of folate and other vitamins, thus controlling plasma homocysteine levels, and reducing intake of types A1 and B casein. High intake of these forms of casein is thought to be associated with diabetes. The immunological properties of beta-**casomorphin** 9 are discussed. This is a relatively stable peptide digest fraction of A2 beta-casein.

L3 ANSWER 4 OF 4 FROSTI COPYRIGHT 2004 LFRA on STN  
ACCESSION NUMBER: 545303 FROSTI  
TITLE: Prophylactic dietary supplement based on milk.  
INVENTOR: Elliott R.B.; Laugesen B.M.  
PATENT ASSIGNEE: New Zealand Milk Institute Ltd  
SOURCE: PCT Patent Application  
PATENT INFORMATION: WO 2001000047 A1  
APPLICATION INFORMATION: 20000629  
PRIORITY INFORMATION: New Zealand 19990629; 20000418  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
SUMMARY LANGUAGE: English

AB A fortified milk product is described, for use as a dietary supplement. It contains cobalamin (vitamin V12), pyridoxine, folic acid, and betaine, with a casein fraction limited to Type 2 casein. The invention provides for manufacture of treated milk products and cereals. The supplement is intended to be used in control of diabetes and in reducing risk of **cardiovascular** disease. This may be achieved by treating an underlying deficiency of folate and other vitamins, thus controlling plasma homocysteine levels, and reducing intake of types A1 and B casein. High intake of these forms of casein is thought to be associated with diabetes. The immunological properties of beta-**casomorphin** 9 are discussed. This is a relatively stable peptide digest fraction of A2 beta-casein.

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- antiarrhythmic and coronary dilating actions, increase the expression of high affinity ouabain binding sites and modulate the functional properties of the myocardial beta-adrenoceptor G-protein complex. In the present study, the peptides (including 2-, 3- and 4-D-amino acid substituted beta-casomorphin analogs and partial amino acid sequences such as Pro-Gly and Tyr-Pro-Phe) protected isolated perfused guinea-pig heart and atria from various experimental injuries. **Cardioprotection** was possibly mediated by an influence on membrane integrity, receptor susceptibility and ion fluxes, and was especially effective in the depolarized myocardium. (congress abstract).

ABEX Experiments were performed with damaged preparations of auricles and isolated perfused hearts of guinea-pigs. Substances derived by substitution of beta-casomorphin by D-amino acids in the 2-, 3- or 4-positions exerted comparable cardiac effects. A similar efficacy was seen with compounds with partial amino acid sequences (e.g. Pro-Gly and Tyr-Pro-Phe). Experimentally induced cardiac injuries (provoked by hypoxia, calcium deficiency, potassium excess and PAF) provoked a significant reduction in cardiac performance up to 50-70% of the initial value. Under these conditions the investigated peptides markedly improved or even restored cardiac function. (NPH)

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> d 18

L8 ANSWER 1 OF 4 REGISTRY COPYRIGHT 2004 ACS on STN

RN 157173-37-0 REGISTRY

CN L-Asparagine, L-tyrosyl-L-prolyl-L-phenylalanyl-L-prolylglycyl-L-prolyl-L-isoleucyl-L-prolyl- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN L-Asparagine, N2-[1-[N-[1-[N-[1-[N-(1-L-tyrosyl-L-prolyl)-L-phenylalanyl]-L-prolyl]glycyl]-L-prolyl]-L-isoleucyl]-L-prolyl]-

OTHER NAMES:

CN **Bovine [Pro8]- $\beta$ -casomorphin-9**

FS PROTEIN SEQUENCE; STEREOSEARCH

MF C50 H68 N10 O12

SR CA

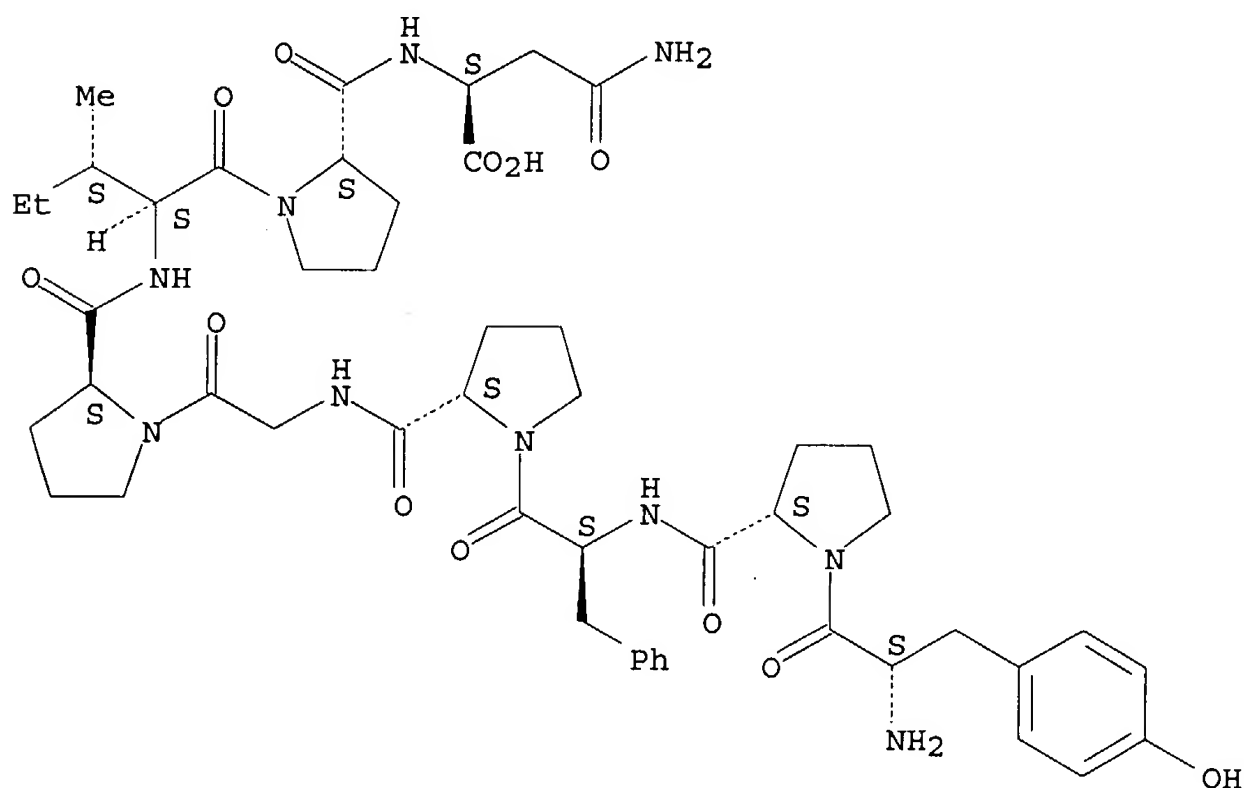
LC STN Files: CA, CAPLUS, CASREACT, TOXCENTER

DT.CA Caplus document type: Journal; Patent

RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

RL.NP Roles from non-patents: BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process); PRP (Properties)

Absolute stereochemistry.



5 REFERENCES IN FILE CA (1907 TO DATE)

5 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=>



-e.casomorphin-9/cn

E1	1	CASOMORPHIN, PRO-/CN
E2	1	CASOMORPHIN, PRO- (OX)/CN
E3	0 -->	CASOMORPHIN-9/CN
E4	1	CASOMORPHINASE/CN
E5	1	CASORON/CN
E6	1	CASORON 133/CN
E7	1	CASORON G/CN
E8	1	CASOXIN 4/CN
E9	1	CASOXIN 5/CN
E10	1	CASOXIN 6/CN
E11	1	CASOXIN C/CN
E12	1	CASOXIN D/CN

=> d ibib abs 17 1-4

L7 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1990:179897 CAPLUS

DOCUMENT NUMBER: 112:179897

TITLE: Preparation of **casomorphin analogs**  
as **cardiovascular** agents

INVENTOR(S): Neubert, Klaus; Mentz, Peter; Barth, Alfred; Liebmann,  
Claus; Schrader, Uwe; Hartrodt, Bianca; Born, Ilona;  
Luecke, Lothar; Stoeckel, Christian; et al.

PATENT ASSIGNEE(S): VEB Fahlberg-List, Ger. Dem. Rep.

SOURCE: Ger. (East), 23 pp.

CODEN: GEXXA8

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DD 272227	A1	19891004	DD 1988-315831	19880517
PRIORITY APPLN. INFO.:			DD 1988-315831	19880517

OTHER SOURCE(S): CASREACT 112:179897

AB **Cardioactive** prepn. containing **casomorphin**  
**analog**s at 10-9-10-7M were prepared Thus, H-Tyr-Pro-D-Phe-Pro-Gly-  
OH.HCl, prepared by the solution phase method, at 10-9M in guinea pig auricle  
increased cardiac performance (product of contractile amplitude and  
frequency) by 20%.

L7 ANSWER 2 OF 4 DDFB COPYRIGHT 2004 THE THOMSON CORP on STN

ACCESSION NUMBER: 1980-36366 P A

TITLE: CARDIOVASCULAR EFFECTS OF PEPTIDES RELATED TO THE ENKEPHALINS  
AND BETA-CASOMORPHIN.

AUTHOR: WEI E T; LEE A; CHANG J K

LOCATION: BELMONT, CAL., USA.

SOURCE: LIFE SCI. (26, NO.18, 1517-22, 1980)

LANGUAGE: English

L7 ANSWER 3 OF 4 DRUGB COPYRIGHT 2004 THE THOMSON CORP on STN

ACCESSION NUMBER: 1980-36366 P A

TITLE: CARDIOVASCULAR EFFECTS OF PEPTIDES RELATED TO THE ENKEPHALINS  
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AUTHOR: WEI E T; LEE A; CHANG J K

LOCATION: BELMONT, CAL., USA.

SOURCE: LIFE SCI. (26, NO.18, 1517-22, 1980)

LANGUAGE: English

L7 ANSWER 4 OF 4 DRUGU COPYRIGHT 2004 THE THOMSON CORP on STN

ACCESSION NUMBER: 1992-15100 DRUGU P

TITLE: Effects of beta-Casomorphin and Related Peptides in  
Experimentally Induced Cardiac Injuries.

AUTHOR: Mentz P; Neubert K; Liebmann C; Hoffmann S; Barth A

LOCATION: Halle, Germany, West

SOURCE: Arch. Pharmacol. (344, Suppl. 2, R120, 1991)

CODEN: NSAPCC ISSN: 0028-1298

AVAIL. OF DOC.: Dept. of Pharmacology and Toxicology, Martin-Luther  
University Halle, Leninallee 4, 0-4020 Halle/S, Germany.

LANGUAGE: English

DOCUMENT TYPE: Journal

FIELD AVAIL.: AB; LA; CT; MPC

FILE SEGMENT: Literature

AN 1992-15100 DRUGU P

AB Beta-casomorphin and related peptides exert positive inotropic,

DERWENT-ACC-NO: 1990-076196

DERWENT-WEEK: 199011

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TITLE: Cardioactive compsn. contg.  
casomorphine type peptide or  
derivs. - to strengthen heart beat,  
normalise cardiac rhythm and improve myocardial blood  
flow

INVENTOR: BARTH, A; BORN, I ; HARTRODT, B ; LIEBMANN, C D ;  
LUCKE, L ; MENTZ, P  
; NEUBERT, K ; SCHRADER, U

PATENT-ASSIGNEE: VEB FAHLBERG-LIST M[VEFL]

PRIORITY-DATA: 1988DD-0315831 (May 17, 1988)

PATENT-FAMILY:

PUB-NO	PAGES	PUB-DATE	
LANGUAGE		MAIN-IPC	
DD 272227 A		October 4, 1989	N/A
021	N/A		

APPLICATION-DATA:

PUB-NO	APPL-DESCRIPTOR	APPL-NO
APPL-DATE		
DD 272227A	N/A	1988DD-
0315831	May 17, 1988	

INT-CL (IPC): A61K037/02

ABSTRACTED-PUB-NO: DD 272227A

BASIC-ABSTRACT:

Cardio-active compsn. contains as active ingredient a  
casomorphine-type peptide  
(I), or its deriv., at concn. of 1-100 nmoles/l or 1-1000  
microg/kg.

USE/ADVANTAGE - (I) strengthen the heart beat, normalise cardiac rhythm and improve blood flow in the myocardium, so are useful in treatment of cardiac insufficiency and angina pectoris. They are well tolerated and can also be added (at 0.1-1%) to known cardiogenic, antianginal and antiarrhythmic compounds. to improve their activity. (I) are administered intravenously, intraperitoneally, orally or by infusion. The activity of (I) can be increased/prolonged by incorporation of D-amino acids; the compounds are resistant to enzymatic breakdown; specified changes in structure can alter the activity profile, and modification of lipophilic and other physicochemical properties can improve transport and penetration properties.

CHOSEN-DRAWING: Dwg.0/0

TITLE-TERMS: CARDIOACTIVE COMPOSITION CONTAIN TYPE PEPTIDE  
DERIVATIVE STRENGTH  
HEART BEAT NORMALISE CARDIAC RHYTHM IMPROVE  
MYOCARDIUM BLOOD FLOW

DERWENT-CLASS: B04

CPI-CODES: B04-C01A; B12-F01; B12-F02;

CHEMICAL-CODES:

Chemical Indexing M1 \*01\*

Fragmentation Code

F012 F423 G010 G013 G100 H1 H100 H181 H4 H401  
H441 H598 H8 J0 J011 J1 J111 J171 J311 J371  
M210 M211 M271 M280 M281 M311 M312 M314 M320 M321  
M331 M332 M333 M340 M342 M343 M349 M371 M381 M391  
M423 M510 M520 M530 M531 M540 M620 M781 M903 P521  
P522 P523 V902 V911 V921 V925

Registry Numbers

1327U 0502U

SECONDARY-ACC-NO:

CPI Secondary Accession Numbers: C1990-033359